

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/009263

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/20 C07C311/29 C07C311/43 A61K31/18 A61P19/02
A61P35/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/44711 A (AMERICAN CYANAMID COMPANY) 3 August 2000 (2000-08-03) page 10, line 19 - line 26; examples 18,26,32; table 1	1-4,7, 14-20, 23,24, 27,28, 30,31, 33-36, 38-40
A	WO 97/44315 A (WARNER-LAMBERT) 27 November 1997 (1997-11-27) page 21, line 16 - page 22, line 2; claims 1,14,16	1-40
A	WO 00/63165 A (FUJISAWA PHARMACEUTICAL) 26 October 2000 (2000-10-26) page 1 - page 3; examples 33,43	1-40

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

22 June 2005

Date of mailing of the international search report

08/07/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 661 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009263

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international Application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/009263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0044711	A	03-08-2000	AU 769410 B2 29-01-2004
			AU 2630600 A 18-08-2000
			BR 0007754 A 13-11-2001
			CA 2356345 A1 03-08-2000
			CN 1337944 A 27-02-2002
			CZ 20012709 A3 17-04-2002
			EP 1147078 A1 24-10-2001
			HU 0200605 A2 29-07-2002
			JP 2002535383 T 22-10-2002
			NO 20013639 A 24-07-2001
			NZ 512025 A 29-08-2003
			WO 0044711 A1 03-08-2000
			ZA 200104508 A 02-09-2002
WO 9744315	A	27-11-1997	AT 207891 T 15-11-2001
			AU 713286 B2 25-11-1999
			AU 2680397 A 09-12-1997
			BG 63940 B1 31-07-2003
			BG 102918 A 30-09-1999
			BR 9710841 A 17-08-1999
			CA 2253342 A1 27-11-1997
			CN 1219166 A ,C 09-06-1999
			CZ 9803668 A3 17-02-1999
			DE 69707865 D1 06-12-2001
			DE 69707865 T2 02-05-2002
			DK 901466 T3 18-02-2002
			EA 1561 B1 23-04-2001
			EE 9800397 A 15-06-1999
			EP 0901466 A1 17-03-1999
			ES 2167733 T3 16-05-2002
			HK 1019585 A1 31-05-2002
			JP 2000511175 T 29-08-2000
			KR 2000011095 A 25-02-2000
			NO 985326 A 14-01-1999
			NZ 332711 A 23-06-2000
			PL 329929 A1 26-04-1999
			PT 901466 T 29-04-2002
			SI 901466 T1 28-02-2002
			SK 157798 A3 13-04-1999
			WO 9744315 A1 27-11-1997
			ZA 9704223 A 10-12-1997
WO 0063165	A	26-10-2000	EP 1171422 A1 16-01-2002
			WO 0063165 A1 26-10-2000
			JP 2002542228 T 10-12-2002

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 19044.0057P1	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2005/009263	International filing date (<i>day/month/year</i>) 21 March 2005 (21.03.2005)	Priority date (<i>day/month/year</i>) 22 March 2004 (22.03.2004)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant SOUTHERN RESEARCH INSTITUTE			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input type="checkbox"/>	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

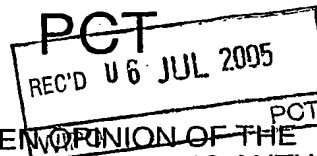
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland		Date of issuance of this report 26 September 2006 (26.09.2006)
Facsimile No. +41 22 338 82 70		Authorized officer Dorothee Mülhausen e-mail: pt01@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/009263

International filing date (day/month/year)
21.03.2005

Priority date (day/month/year)
22.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07C311/20, C07C311/29, C07C311/43, A61K31/18, A61P19/02, A61P35/04

Applicant
SOUTHERN RESEARCH INSTITUTE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

English, R

Telephone No. +31 70 340-2860



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 23-40

because:

- ☒ the said international application, or the said claims Nos. 23-40 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5,6,8-13,21,22,25,26,29,32,37
	No: Claims	1-4,7,14-20,23,24,27,28,30,31,33-36,38-40
Inventive step (IS)	Yes: Claims	5,6,8-13,21,22,25,26,29,32,37
	No: Claims	1-4,7,14-20,23,24,27,28,30,31,33-36,38-40
Industrial applicability (IA)	Yes: Claims	1-22
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

- D1:** WO 00/44711 A (American Cyanamid) 3 August 2000
- D2:** WO 97/44315 A (Warner-Lambert) 27 November 1997
- D3:** WO 00/63165 A (Fujisawa Pharmaceutical) 26 October 2000

1. Subject-matter

The present application concerns certain sulphonamido and sulphonylmethyl hydroxamic acid derivatives in which the two substituents are attached to adjacent carbon atoms of a ring. These compounds are modulators of matrix metalloproteinases and are in particular selective inhibitors of MMP-2 and MMP-9. They are useful in the treatment of tumour metastasis and arthritis.

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4,7,14-20,23,24,27,30,31,33-36,38-40 is not new in the sense of Article 33(2) PCT.

Document D1 discloses certain compounds which are shown to be suitable for the treatment of arthritis and tumour metastasis (page 10, lines 19-26; table 1). The compounds of claims 18,26,32 are compounds of the present invention in which R is a phenyl group substituted in the 4-position by a 2-butyloxy group, X is a CH₂ (examples

18,32) or CH_2CH_2 (example 26) group and Z is a NH group.

Thus, the subject-matter of "compound" claims 1-4,7 and "use" claims 14-20,23,24, 27,30,31,33-36,38-40 does not appear to be new.

3. Inventive step

In the absence of novelty of the subject-matter of claims 1-4,7,14-20,23,24,27,28,30, 31,33-36,38-40, no inventive step can be acknowledged for these claims.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 5,6,9-13 and claims 14-40 in so far as they relate to the use of the compounds of these claims, and discloses the use of certain benzenesulphonylamido hydroxamic acid derivatives in the treatment of arthritis and tumour metastasis (see paragraph 3 above). The benzenesulphonylamido hydroxamic acid derivatives explicitly disclosed in D1 (examples 18,26,32) differ from those of the present invention in that the former have a 2-butyloxy group attached to the phenyl ring of the benzenesulphonylamido group, whilst the latter have a bromo group, a methoxy group or a phenyl-containing group attached to this phenyl group.

A comparison of the pharmaceutical data in the present invention (page 38, table 1) with that in D1 (page 41, table 1) shows that the compounds 2c and 1c of the present invention are substantially more active as inhibitors of MMP-9 than the closest compounds of D1 (examples 18,26,32). The problem to be solved by the present invention may therefore be regarded as the provision of improved MMP modulators suitable for the treatment of cancer and arthritis. The applicant solves this problem by means of the compounds of claim 5.

It is known from D1 that 2-(4-butyloxybenzenesulphonamido)cyclohexane- hydroxamic acids are useful in the treatment of cancer and arthritis. It is also known from documents D2 and D3 that biphenylsulphonamido (D2, claims 1,14,16; page 21, line 16 - page 22, line 2) and 4-phenoxybenzenesulphonamido hydroxamic acid derivatives (D3, pages 1-3; examples 33,43) are useful in the treatment of cancer and arthritis. However, it would not be obvious to the person skilled in the art that replacing the butyloxy group of the compounds of D1 with the phenyl or phenoxy group of the compounds of D2 and D3

would lead to compounds which are more active in inhibiting MMP-9.

Consequently, the subject-matter of claims 5,6,9-13 and claims 14-40 in so far as they relate to the use of the compounds of these claims appears to involve an inventive step and to satisfy the requirements of Article 33(3) PCT.

4. Industrial applicability

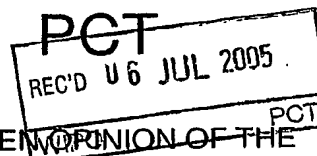
For the assessment of the present claims 23-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/009263

International filing date (day/month/year)
21.03.2005

Priority date (day/month/year)
22.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07C311/20, C07C311/29, C07C311/43, A61K31/18, A61P19/02, A61P35/04

Applicant
SOUTHERN RESEARCH INSTITUTE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

English, R

Telephone No. +31 70 340-2860



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. 1 Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 23-40

because:

- ☒ the said international application, or the said claims Nos. 23-40 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009263

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5,6,8-13,21,22,25,26,29,32,37
	No: Claims	1-4,7,14-20,23,24,27,28,30,31,33-36,38-40
Inventive step (IS)	Yes: Claims	5,6,8-13,21,22,25,26,29,32,37
	No: Claims	1-4,7,14-20,23,24,27,28,30,31,33-36,38-40
Industrial applicability (IA)	Yes: Claims	1-22
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

- D1:** WO 00/44711 A (American Cyanamid) 3 August 2000
- D2:** WO 97/44315 A (Warner-Lambert) 27 November 1997
- D3:** WO 00/63165 A (Fujisawa Pharmaceutical) 26 October 2000

1. Subject-matter

The present application concerns certain sulphonamido and sulphonylmethyl hydroxamic acid derivatives in which the two substituents are attached to adjacent carbon atoms of a ring. These compounds are modulators of matrix metalloproteinases and are in particular selective inhibitors of MMP-2 and MMP-9. They are useful in the treatment of tumour metastasis and arthritis.

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 7, 14-20, 23, 24, 27, 30, 31, 33-36, 38-40 is not new in the sense of Article 33(2) PCT.

Document D1 discloses certain compounds which are shown to be suitable for the treatment of arthritis and tumour metastasis (page 10, lines 19-26; table 1). The compounds of claims 18, 26, 32 are compounds of the present invention in which R is a phenyl group substituted in the 4-position by a 2-butoxy group, X is a CH₂ (examples

18,32) or CH_2CH_2 (example 26) group and Z is a NH group.

Thus, the subject-matter of "compound" claims 1-4,7 and "use" claims 14-20,23,24, 27,30,31,33-36,38-40 does not appear to be new.

3. Inventive step

In the absence of novelty of the subject-matter of claims 1-4,7,14-20,23,24,27,28,30, 31,33-36,38-40, no inventive step can be acknowledged for these claims.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 5,6,9-13 and claims 14-40 in so far as they relate to the use of the compounds of these claims, and discloses the use of certain benzenesulphonylamido hydroxamic acid derivatives in the treatment of arthritis and tumour metastasis (see paragraph 3 above). The benzenesulphonylamido hydroxamic acid derivatives explicitly disclosed in D1 (examples 18,26,32) differ from those of the present invention in that the former have a 2-butynoxy group attached to the phenyl ring of the benzenesulphonylamido group, whilst the latter have a bromo group, a methoxy group or a phenyl-containing group attached to this phenyl group.

A comparison of the pharmaceutical data in the present invention (page 38, table 1) with that in D1 (page 41, table 1) shows that the compounds 2c and 1c of the present invention are substantially more active as inhibitors of MMP-9 than the closest compounds of D1 (examples 18,26,32). The problem to be solved by the present invention may therefore be regarded as the provision of improved MMP modulators suitable for the treatment of cancer and arthritis. The applicant solves this problem by means of the compounds of claim 5.

It is known from D1 that 2-(4-butynoxybenzenesulphonamido)cyclohexane- hydroxamic acids are useful in the treatment of cancer and arthritis. It is also known from documents D2 and D3 that biphenylsulphonamido (D2, claims 1,14,16; page 21, line 16 - page 22, line 2) and 4-phenoxybenzenesulphonamido hydroxmic acid derivatives (D3, pages 1-3; examples 33,43) are useful in the treatment of cancer and arthritis. However, it would not be obvious to the person skilled in the art that replacing the butynoxy group of the compounds of D1 with the phenyl or phenoxy group of the compounds of D2 and D3

would lead to compounds which are more active in inhibiting MMP-9.

Consequently, the subject-matter of claims 5,6,9-13 and claims 14-40 in so far as they relate to the use of the compounds of these claims appears to involve an inventive step and to satisfy the requirements of Article 33(3) PCT.

4. Industrial applicability

For the assessment of the present claims 23-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.